REMARKS

This amendment is responsive to the non-final Office Action mailed March 10, 2004. Claims 122-150 were pending in the instant Application. In this amendment, Claims 142, 144, and 146 are cancelled without prejudice to Applicants' right to pursue the subject matter of the cancelled claims in one or more related continuation, divisional or continuation-in-part application(s) and Claims 122, 124, 126, 127, 130-134, 137-139, 143, 145, and 150 are amended. Thus, following entry of the present amendment, Claims 122-141, 143, 145, and 147-150 will be pending and under consideration.

I. The Amendment to the Claims

In the present amendment, Claims 142, 144, and 146 are cancelled and Claims 122, 124, 126, 127, 130-134, 137-139, 143, 145, and 150 are amended. The amendments to Claims 122, 124, 126, 127, 130-134, 137-139, 143, 145, and 150 are fully supported by the specification and claims of the application as originally filed.

In particular, support for the amendment to Claim 122 can be found, for example, in Claims 98 and 100 as originally filed and in the specification at page 60, lines 1-17. Support for the amendment to Claim 124 can be found, for example, in Claim 107 as originally filed and at page 164, line 28 to page 165, line 3. Support for the amendment to Claim 126 can be found, for example, in Claim 117 as originally filed and in the specification at page 167, lines 11-28.

Support for the amendment to Claim 127 can be found, for example, in Claim 98 as originally filed and in the specification at page 60, lines 1-17. Support for the amendment to Claim 130 can be found, for example, in Claim 101 as originally filed and in the specification at page 163, lines 2-19. Support for the amendment to Claim 131 can be found, for example, in Claim 102 as originally filed and in the specification at page 163, lines 21-29. Support for the amendment to Claim 132 can be found, for example, in Claim 104 as originally filed and in the specification at page 164, lines 7-11.

Support for the amendment to Claim 133 can be found, for example, in Claim 105 as originally filed and in the specification at page 164, lines 13-19. Support for the amendment to Claim 134 can be found, for example, in Claim 107 as originally filed and in the specification at page 164, line 28, to page 165, line 3. Support for the amendment to Claim 137 can be found, for example, in Claim 112 as originally filed and in the specification at page 166, lines 1-10. Support for the amendment to Claim 138 can be found, for example, in Claim 199 as originally filed and in the specification at page 168, lines 5-15. Support for the

amendment to Claim 139 can be found, for example, in Claims 103, 106, 111, and 120 as originally filed and in the specification at page 163, line 31 to page 164, line 4, at page 164, lines 21-26, at page 165, lines 27-33, and at page 168, lines 17-23.

Support for the amendment to Claim 143 can be found, for example, in Claim 103 as originally filed and in the specification at page 163, line 31 to page 164, line 4. Support for the amendment to Claim 145 can be found, for example, in Claim 113 as originally filed and in the specification at page 166, lines 11-17. Finally, support for the amendment to Claim 150 can be found, for example, in Claim 121 as originally filed and in the specification at page 89, line 7 to page 93, line 29, particularly at page 91, line 34 to page 95, line 24.

Further support for the amendments to Claims 122, 124, 126, 127, 130-134, 137-139, 143, 145, and 150 is provided 122, 124, 126, 127, 130-134, 137-139, 143, 145, and 150 as presented in the amendment and response filed November 14, 2003. Claims 122, 124, 126, 127, 130-134, 137-139, 143, 145, and 150 were entered in to the record of the present application without objection in the Office Action mailed March 10, 2004, indicating that the PTO considered this amendment to be fully supported by the application as filed.

Applicants note that Claims 122, 124, 126, 127, 130-134, 137, and 150 recite groups of secondary mutations that are smaller than the groups of secondary mutations recited by the claims as originally filed. For example, Claim 122 as amended recites a reduced group of secondary mutations in comparison to Claim 122 as originally filed. Although the groups of secondary mutations are reduced in number, each member of each group of secondary mutations presented by the new claims is recited in a single group by the specification and at least one claim. Thus, the reduced groups of secondary mutations recited by Claims 122, 124, 126, 127, 130-134, 137, and 150 are supported by the larger sets of secondary mutations described in the application as originally filed.

In support of Applicants' contention that the larger groups of secondary mutations recited by the as-filed claims provide adequate description for the claims presented in the instant amendment, Applicants respectfully invite the PTO's attention to M.P.E.P. § 2173.05(i). Here, the M.P.E.P. explains that "[i]f alternative elements are positively recited in the specification, they may be explicitly excluded in the claims." *See* M.P.E.P. § 2173.05(i). The legal basis for this rule is found in *In re Johnson* 558 F.2d 1008, 194 U.S.P.Q. 187 (C.C.P.A., 1977). In *In re Johnson*, the Applicants described a genus of chemical compounds in the application as filed, then claimed a subgenus of the compounds that lacked word-for-word support in the application as filed. The Court of Customs and Patent Appeals held that "the specification, having described the whole [genus], necessarily

described the [subgenus] remaining." *See In re Johnson* 558 F.2d 1008, 1019, 194 U.S.P.Q. 187, 196 (C.C.P.A., 1977). Thus, Applicants respectfully submit that *In re Johnson* and M.P.E.P. § 2173.05(i) show that the larger groups of secondary mutations described by the application as filed support the smaller groups of secondary mutations recited by Claims 127-138 as presented in the instant amendment.

In view of the foregoing, Applicants respectfully submit that the amendments to Claims 122, 124, 126, 127, 130-134, 137-139, 143, 145, and 150 are fully supported by the specification and claims of the application as originally filed. Accordingly, no new matter is introduced by the instant amendment. Therefore, Applicants hereby respectfully request entry of the present amendment under 37 C.F.R. § 1.111.

II. The Rejection of Claims 122-150 under 35 U.S.C. § 112, Second Paragraph, Should Be Withdrawn

Claims 122-150 stand rejected under 35 U.S.C. 112, second paragraph, as allegedly indefinite on several bases. First, the PTO contends that the steps of Claims 122, 126, 127, 138, 139, and 149, directed to methods for assessing the effectiveness of protease antiretroviral therapy, do not have a clear point that ties to the effectiveness of the antiretroviral therapy. Second, the PTO argues that the subject matter claimed in Claims 131-137 as previously pending conflicts with the subject matter claimed in Claims 139-149. Third, the PTO asserts that Claims 124, 125, 130-134, 136, 137, 142-145, 147, and 148 recite terms that lack antecedent basis. Fourth, the PTO contends that the nexus between expression of the indicator gene and activity of the HIV protease as recited by Claim 150 is not clear. In response, Applicants respectfully submit that certain of these rejections are moot in view of the amendments to or cancellation of the claims presented in the present response, and that others of these rejections are not supported by the appropriate legal standard.

A. The Legal Standard

Under 35 U.S.C. § 112, second paragraph, a claim must particularly point out and distinctly claim the subject matter which the applicant regard as his invention. *See* 35 U.S.C. § 112, second paragraph. This statutory mandate is met when "one skilled in the art would understand the bounds of the claim when read in light of the specification." *See Solomon v. Kimberly-Clark Corporation*, 216 F.3d 1372, 1378, 55 USPQ2d 1279, 1282 (Fed. Cir., 2000), quoting *Personalized Media Communications, LLC v. International Trade Commission et al.*, 161 F.3d 696, 705, 48 USPQ2d 1880, 1888 (Fed. Cir., 1998). "If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 demands no more." *See Personalized Media*, 161 F.3d at 705, 48

USPQ2d at 1888, quoting *Miles Lab., Inc. v. Shandon, Inc.* 997 F.2d 870, 238 USPQ2d 1123 (Fed. Cir., 1993).

B. <u>One of Skill in the Art Can Understand the Scope of Claims 122-141, 143, 145, and 147-150</u>

Applicants respectfully submit that a skilled artisan can readily understand the scope of Claims 122-141, 143, 145, and 147-150 as amended in the present response, and therefore these claims are not indefinite under 35 U.S.C. § 112, second paragraph.

First, Applicants respectfully submit that one of skill in the art can understand how the steps of Claims 122, 126, 127, 138, 139, and 149 allow a practitioner to assess the effectiveness of the antiretroviral therapy as recited by the preamble to these claims when the claims are read in light of the specification. In particular, Claims 122, 126, 127, 138, 139, and 149 each comprise a single step that entails, *inter alia*, detecting in a sample from an HIV-infected patient the presence of a nucleic acid encoding HIV protease that comprises mutations in certain combinations of codons of the HIV protease. The specification teaches correlations between the presence of such mutations and resistance or susceptibility of the HIV infecting the patient to particular HIV protease inhibitors. *See*, for example, Tables 13-27 at pages 182-189 of the specification.

For example, Table 21 at page 186 indicates that the presence of a mutation in codon 90 in combination with a mutation in one of 13 other specific codons significantly correlates with saquinavir resistance, while the presence mutations in codon 90 in combination with mutations in one of three other codons significantly correlates with saquinavir susceptibility. If a practitioner detects a combination of mutations that correlates with resistance to saquinavir, the practitioner would recognize that saquinavir therapy would not be effective. Similarly, if the practitioner detects a combination of mutations that correlates with susceptibility to saquinavir, the practitioner would recognize that saquinavir therapy would be effective.

In either case, detecting the presence of mutations associated with protease inhibitor resistance or susceptibility allows the skilled artisan to evaluate whether protease inhibitor therapy would be effective. Thus, detecting the presence of the mutations associated with resistance would allow the practitioner to assess the effectiveness of protease anti-retroviral therapy, whether such therapy had been performed in the past, is currently being administered, or is contemplated for administration at some point in the future. Therefore, the steps of the methods of Claims 122, 126, 127, 138, 139, and 149 do allow a skilled artisan to

accomplish the purpose set forth in the preambles to these claims, and are accordingly not indefinite under 35 U.S.C. § 112, second paragraph.

Second, without acquiescing to the propriety of the rejection of Claims 131-137 and 139-149 as directed to conflicting subject matter, Applicants respectfully submit that the rejection is moot in view of the amendments to Claims 139, 143, and 145, and cancellation of Claims 142, 144, and 146. Accordingly, Applicants respectfully submit that Claims 131-137 and Claims 139-141, 143, 145, and 147-149 are not directed to conflicting subject matter. Accordingly, Applicants respectfully submit that Claims 131-137 and 139-141, 143, 145, and 147-149 are not indefinite under 35 U.S.C. § 112, second paragraph.

Third, Applicants respectfully submit that each of the terms recited by Claims 124, 125, 130-134, 136, 137, 142-145, 147, and 148 that allegedly lack antecedent basis in fact find antecedent in a claim from which the rejected claims depend. Claims 124, 130-134, 136, 137, 142, 143, 145, and 148 each recite the limitation "said nucleic acid." The limitation "said nucleic acid" recited by Claim 124 finds antecedent support in line 3 of Claim 122 ("detecting ... a nucleic acid"), from which it depends. Similarly, the antecedent basis for this limitation as recited by Claims 130-134, 136, 137 is in line 3 of Claim 127 ("detecting ... a nucleic acid"), from which each of these claims ultimately depends. Likewise, the antecedent basis for this limitation as recited by Claims 142, 143, 145, 148 is in line 3 of Claim 139 ("detecting ... a nucleic acid"), from which each of these claims ultimately depends.

In addition, Claim 125 recites the limitation "said difference," alleged to lack antecedent basis in the claim. The antecedent basis for this limitation is found in lines 9 and 10 of Claim 122 ("a difference in said HIV protease's susceptibility to amprenavir..."), from which Claim 125 ultimately depends. Finally, Claim 147 recites the limitation "said increase," alleged to lack antecedent basis in the claim. Such antecedent basis is found in line 10 of Claim 139 ("an increase in said HIV's susceptibility..."), from which Claim 147 depends. Thus, each of the terms asserted to lack antecedent basis recited by Claims 124, 130-134, 136, 137, 142, 143, 145, and 147 in fact find antecedent support in a claim from which the rejected claims depend. Accordingly, Applicants respectfully submit that Claims 124, 130-134, 136, 137, 142, 143, 145, and 147 are not indefinite under 35 U.S.C. § 112, second paragraph.

Finally, Claim 150 stands rejected as allegedly indefinite because the nexus between protease activity and expression of the indicator gene is not clear to the PTO. In particular, the PTO requests clarification as to what the indicator gene is indicating, what is affecting the

activity of the HIV protease, and how the amount of expression of the indicator gene is determined. Claim 150 recites a test vector that comprises, *inter alia*, an indicator gene and a segment encoding HIV protease, wherein the amount of expression of the indicator gene depends on the activity of the HIV protease. Applicants respectfully submit that one of skill in the art can readily understand the scope of Claim 150 in light of the specification.

The specification teaches that the indicator gene indicates the activity of the HIV protease and reverse transcriptase encoded by the segment. *See*, for example, the specification at pages 69-77. Here, the specification provides an extensive discussion of the indicator gene and how the expression of the indicator gene depends on the action of a gene encoded by a nucleic acid segment encoding viral genes, *e.g.*, HIV protease. Thus, the amount of expression of the indicator gene indicates the activity of genes encoded by the segment derived from HIV, and allows the skilled artisan to assess such activity, for example, in the presence and absence of HIV protease inhibitors. For example, differences in HIV protease activity, *e.g.*, differences in expression or catalytic action, are reflected in similar differences in expression of the indicator gene, which can be readily observed by a skilled artisan.

By performing such assessments of HIV protease activity, the skilled artisan can determine the susceptibility or resistance of the HIV to HIV protease inhibitors. Thus, the effects of the protease inhibitors on HIV protease can be conveniently determined by monitoring expression of the indicator gene. The amount of expression of the indicator gene can be determined by any method or assay appropriate to the indicator gene selected. The specification, at pages 69-70 provides a number of examples of suitable indicator genes, including, but not limited to, a preferred indicator gene, luciferase. As one of skill in the art will readily recognize, luciferase expression can be detected, for example, by monitoring fluorescence emitted by this enzyme. Thus, one of skill in the art can readily determine an amount of expression of an indicator gene by, for example, assessing indicator gene activity.

Finally, Applicants note that a skilled artisan can readily recognize the metes and bounds of Claim 150, as required by the legal standard set forth above. Claim 150 recites a test vector comprising, *inter alia*, a segment encoding HIV protease derived from HIV infecting a patient and an indicator gene, wherein the amount of expression of the indicator gene depends on the activity of the HIV protease. The skilled artisan can recognize a vector that comprises such a segment encoding HIV protease, such an indicator gene, and the relationship between activity of the HIV protease and expression of the indicator gene. Thus,

the ordinarily skilled artisan can recognize the metes and bounds of Claim 150 as currently pending.

In view of the foregoing, Applicants respectfully submit that Claims 122-141, 143, 145, and 147-150 are not indefinite and that the rejection of Claims 142, 144, and 146 is moot in view of the cancellation of these claims, and earnestly request that the rejection under 35 U.S.C. § 112, second paragraph, be withdrawn.

III. The Rejection of Claims 122-130 and 138-149 under 35 U.S.C. § 112, First Paragraph, as not Enabled by the Specification Should be Withdrawn

Claims 122-130 and 138-149 stand rejected as allegedly failing to comply with the enablement requirement. Without acquiescing to the propriety of the rejection, Applicants respectfully submit that the present application enables the full scope of Claims 122-130, as set forth below, and respectfully submit that the rejection of Claims 138-149 is moot in view of the amendments to or cancellation of the claims.

A. The Legal Standard

To satisfy 35 U.S.C. § 112, first paragraph, a specification must, *inter alia*, describe a claimed invention sufficiently to enable one of ordinary skill in the art to practice the invention without undue experimentation. *See In re Wands*, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1988). The multi-factor test summarized by the Federal Circuit in *Wands* forms the basis for an inquiry into whether an amount of experimentation is undue.

The *Wands* factors include (1) the quantity of experimentation necessary, (2) the amount of guidance provided, (3) the presence or absence of working examples, (4) the nature of the invention, (5), the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *See id.* The test for determining whether experimentation is undue is "not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine or the specification provides a reasonable amount of guidance with respect to ... the experimentation." *See Ex parte Jackson*, 217 U.S.P.Q. 804, 807 (1982).

Finally, the PTO must establish a *prima facie* case of non-enablement in order to properly reject a claim on that basis. "When rejecting a claim under the enablement requirement of § 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention in the specification of the application..." *In re Wright*, 27 U.S.P.Q.2d 1510, 1513 (Fed. Cir. 1993). The PTO's *prima*

facie case should address each of the *Wands* factors since "[i]t is improper to conclude that a disclosure is not enabling based on an analysis of only one of the [*Wands*] factors while ignoring one or more of the others." *See* MPEP § 2164.01(a), citing *Wands* at 1407. Where the PTO does not provide evidence regarding one or more *Wands* factors, Applicants presume that such factors support the conclusion that the claims at issue are fully enabled.

B. The Present Application Enables the Full Scope of Claims 122-130

The PTO contends that undue experimentation would be required to practice the full scope of Claims 122-130 since, according to the PTO, the examples and the art allegedly teach that the recited mutations are associated with decreased, not increased susceptibility to protease inhibitors. Applicants believe that the PTO's rejection is founded on a misapprehension that all of the particular combinations of mutations recited by Claims 122-130 correlate with decreased susceptibility to protease inhibitors. In fact, while the examples and the art do teach that certain of the recited combinations of mutations are associated with reduced susceptibility to protease inhibitors, the examples also teach that certain recited combinations of mutations are actually associated with increased susceptibility to protease inhibitors.

For example, Example 17(b) at page 174, lines 6-11 explains that mutations at position 13 in combination with mutations at position 82 correlate with increased indinavir susceptibility rather than decreased indinavir susceptibility. Similarly, Example 17(d) at page 175 explains that mutations at positions 32 or 46 in combination with a mutation at position 82 correlate with increased rather than decreased saquinavir susceptibility. Further examples of combinations of mutations negatively associated with resistance to such protease inhibitors may be found, for example, in Tables 15-21 and 23-26.

Among the codons that correlate with increased susceptibility with protease inhibitors when mutated are codons recited by Claims 122-130. For example, Claims 122 and 126 recite, *inter alia*, detecting a mutation at codon 90 and a mutation at, among others, codon 74. As shown in Table 23, this combination of mutations correlates with increased amprenavir susceptibility, while certain other combinations of mutations recited by Claims 122 and 126 correlate with decreased amprenavir susceptibility. Thus, at least one combination of mutations recited by Claim 122 correlates with increased, not decreased, amprenavir susceptibility. Similarly, Claims 127 and 130 recite, *inter alia*, detecting a combination of a mutation at codon 82 and a mutation at, among others, codon 39. Table 16 indicates that this combination correlates with increased saquinavir susceptibility. Applicants note that the

reference cited by the PTO, Young *et al.*, 1998, *J. Infect. Dis.* 178:1497-1501, does not contradict these results as this reference does not discuss the effects of mutations at position 74 or 39, either alone or in combination with mutations at codon 82.

Thus, a skilled artisan can assess the effectiveness of protease antiretroviral therapy by detecting the specific recited combinations of mutations in light of the teaching of the specification. If the specification teaches that the combination of mutations detected correlates with decreased susceptibility to a particular protease inhibitor, the skilled artisan would assess therapy with that protease inhibitor as having poor effectiveness. Similarly, if the specification teaches that the combination of mutations detected correlates with increased susceptibility to a protease inhibitor, one of skill in the art would assess therapy with that protease inhibitor as being effective. In either case, the presence of the combination of mutations allows the skilled artisan to determine a difference in susceptibility to the protease inhibitor as recited by Claims 122-130. Accordingly, Applicants respectfully submit that the present application enables the skilled artisan to practice the full scope of the invention recited by Claims 122-130.

Parenthetically, Applicants note that the PTO has addressed only one of the eight *Wands* factors, that regarding the scope of the claimed invention. Applicants presume that each of the other *Wands* factors support a conclusion that the present application fully enables one of skill in the art to practice the invention as presently claimed.

In view of the foregoing, Applicants respectfully submit that the rejection of Claims 122-130 and 138-149 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement is either erroneous, as set forth above, or moot in view of the amendments to or cancellation of the claims and earnestly request its withdrawal.

IV. The Rejection of Claims 122-135, 137, and 138 under 35 U.S.C. § 102(b)

Each of Claims 122-135, 137, and 138 stands rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Craig *et al.*, 1998, *AIDS.* 12:1611-1618 ("*Craig*"). In response, and without agreeing to the propriety of the rejection, Applicants respectfully submit the rejection is moot in view of the amendments to or cancellation of the claims. Further, Applicants respectfully submit that *Craig* does not teach each and every element of the invention as presently recited by Claims 122-141, 143, 145, and 147-149. Thus, *Craig* cannot anticipate Claims 122-141, 143, 145, and 147-149 as presently pending.

A. The Legal Standard for Anticipation

The standard governing anticipation under 35 U.S.C. § 102 requires strict identity. *See* M.P.E.P. § 2131. Thus, "for a prior art reference to anticipate in terms of 35 U.S.C. § 102, every element of the claimed invention must be identically shown in a single reference." *See In re Bond*, 15 U.S.P.Q.2d 1566 (Fed. Cir., 1990). Anticipation is not shown even when the differences between the claims and the cited reference are allegedly "insubstantial" and any missing elements could be supplied by the knowledge of one skilled in the art. *See Structural Rubber Prod. Co. v. Park Rubber Co.*, 223 U.S.P.Q. 1264 (Fed. Cir., 1984). Furthermore, in *Jamesbury Corp. v. Litton Industrial Products, Inc.*, 225 U.S.P.Q. 253 (Fed. Cir., 1985), the Federal Circuit explained that even if the prior art teaches "substantially the same thing" as the claimed invention, the reference still cannot anticipate the invention. Thus, a cited reference must describe each and every claim limitation in order to anticipate the invention as claimed.

B. The Cited References do not Teach Each and Every Element of the Invention as Presently Claimed

Craig neither teaches nor suggests any of the methods recited by Claims 122-141, 143, 145, and 147-149. Rather, *Craig* discusses the phenotypes and genotypes of HIV strains isolated from patients that had been treated with saquinavir. Among the phenotypes of such HIV strains assessed by *Craig* is resistance or susceptibility to saquinavir, indinavir, ritonavir, amprenavir, and nelfinavir. *See Craig* at page 1615, table 2. To identify HIV strains resistant to a particular protease inhibitor, *Craig* compares the mean inhibitory concentration (IC_{50}) for a protease inhibitor following saquinavir therapy to baseline values from the same patient. *See id.* Viruses whose mean IC_{50} values for a protease inhibitor increased four-fold were identified as exhibiting significantly reduced susceptibility, *i.e.*, resistant to the protease inhibitor according to *Craig*. *See id.* at page 1614, paragraph bridging pages 1613-1614, final sentence. Thus, a skilled artisan would learn from *Craig* that an HIV exhibiting a mean IC_{50} at least four-fold greater than baseline IC_{50} is resistant to a particular protease inhibitor. Similarly, the skilled artisan would understand from *Craig* that an HIV exhibiting a mean IC_{50} that is not increased at least four-fold over baseline is sensitive to the protease inhibitor.

Of the HIV strains identified in Table 2 of *Craig*, only five exhibit mean IC_{50} values increased greater than four-fold over baseline in the presence of amprenavir. *See id.*, at page 1615, Table 2. None of these HIV strains comprise the specific combination of mutations

presently recited by Claims 122-141, 143, 145, and 147-149. *See id.* For example, HIV isolated from patient 29 comprises mutations at codons 10, 20, 36, 48, 72, 82, 84, 88, and 90 and exhibits a mean IC_{50} increased 6.9 fold over baseline. *See id.* None of Claims 122-149 recite that a mutation at codon 82 or 90 in combination with a mutation at codon 10, 20, 36, 48, 72, 84, or 88 is correlated with resistance to amprenavir.

Similarly, HIV isolated from 22 patients (patients 20-41) exhibit mean IC_{50} values for saquinavir increased at least four-fold over baseline. None of the combinations of mutations found in these resistant HIV strains is recited by Claims 127-141, 143, 145, and 147-149. In fact, none of the specific combinations of mutations found in HIV strains identified as resistant to any protease inhibitor discussed by *Craig* is presently recited by Claims 122-141, 143, 145, and 147-149. Thus, *Craig* does not teach any of the correlations recited by these claims as presently pending. Accordingly, *Craig* cannot anticipate the methods of any of Claims 122-141, 143, 145, or 147-149.

As shown by the foregoing, *Craig* neither teaches nor suggests each element of the methods of assessing the effectiveness of protease antiretroviral therapy in patients by detecting mutations at certain codons of the gene encoding HIV protease in viral nucleic acids recited by Claims 122-141, 143, 145, or 147-149. Accordingly, *Craig* cannot anticipate or render obvious Claims 122-141, 143, 145, or 147-149 under 35 U.S.C. §§ 102(b) or 103(a).

V. The Rejection of Claim 150 as Obvious under 35 U.S.C. § 103(a)

Claim 150 stands rejected as obvious over *Craig* in view of U.S. Patent No. 5,837,464 ("the '464 patent"). Without acquiescing to the propriety of the rejection, and expressly reserving the right to pursue the cancelled subject matter in one or more related continuation, continuation-in-part, or divisional applications, Applicants respectfully submit that the rejection of Claim 150 is moot in view the amendment to Claim 150. Further, Applicants respectfully submit that Claim 150 as amended is not obvious over *Criag* in view of the '464 patent because the cited references, either alone or in combination, do not teach or suggest each and every element of the invention of Claim 150.

A. The Legal Standard

To reject a claim as under 35 U.S.C. § 103(a), the PTO bears the initial burden of showing an invention to be prima facie obvious over the prior art. *See In re Bell*, 26U.S.P.Q.2d 1529 (Fed. Cir. 1992). If the PTO cannot establish a prima facie case of unpatentability, then without more the applicant is entitled to grant of the patent. *See In re*

Oetiker, 24 U.S.P.Q.2d 1443 (Fed. Cir. 1992). The PTO must meet a three-part test to render a claimed invention prima facie obvious.

To begin with, the prior art references cited by the PTO must provide "motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant." *See In re Kotzab*, 55 U.S.P.Q.2d 1316 (Fed. Cir. 2000). Where one reference is relied upon by the PTO, there must be a suggestion or motivation to modify the teachings of that reference. *See id.* Where an obviousness determination rests or relies on the combination of two or more references, there must be some suggestion or motivation to combine the references. *See WMS Gaming Inc. v. International Game Technology*, 51 U.S.P.Q.2d 1386 (Fed. Cir. 1999). The suggestion may be found in implicit or explicit teachings within the references themselves, from the ordinary knowledge of one skilled in the art, or from the nature of the problem to be solved. *See id.*

Second, the prior art references cited by the PTO must suggest to one of ordinary skill in the art that the invention would have a reasonable expectation of success. *See In re Dow Chemical*, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988). The expectation of success, like the motivation to combine two prior art references, must come from the prior art, not the applicant's disclosure. *See id.*

Finally, the PTO must show that the prior art references, either alone or in combination, teach or suggest each and every limitation of the rejected claims. *See In re Gartside*, 53 U.S.P.Q.2d 1769 (Fed. Cir. 2000). If any one of these three factors is not met, the PTO has failed to establish a prima facie case of obviousness and the applicant is entitled to grant of a patent without making any affirmative showing of non-obviousness.

B. *Craig* in Combination with the '464 Patent does not Teach or Suggest Each and Every Element of the Invention

Claim 150 recites a test vector comprising an indicator gene and a segment derived from an HIV-infected patient that further comprises a protease-encoding nucleic acid that has a mutation at codon 82 and a secondary mutation at codon 55, 53, 23, 33, or 59, or a mutation at codon 90 and a secondary mutation at codon 53, 95, 55, 85, 66, 33, 23, or 58. Neither *Craig* nor the '464 patent, either alone or in combination, teach or suggest a test vector comprising protease-encoding nucleic acid that has a mutation at codon 82 or at codon 90 in combination with any of the recited secondary mutations. Thus, an element of Claim 150 is neither taught nor suggested by the cited references, and therefore the PTO cannot make a *prima facie* case of obviousness of Claim 150. Accordingly, Applicants respectfully submit

that Claim 150 is not obvious under 35 U.S.C. § 103(a) and earnestly request passage of the new claims to issuance.

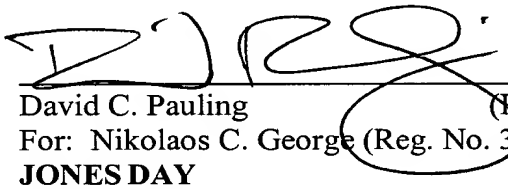
CONCLUSION

In light of the above amendments and remarks, Applicants respectfully submit that Claims 122-141, 143, 145, or 147-150 satisfy all the criteria for patentability and are in condition for allowance. Accordingly, Applicants respectfully request that the Examiner reconsider this application with a view towards allowance and solicit an expeditious passage of Claims 122-141, 143, 145, or 147-150 to issuance. The Examiner is invited to call the undersigned attorney at (212) 790-9090, if a telephone call could help resolve any remaining items.

Pursuant to 37 CFR § 1.136(a)(3), the Commissioner is authorized to charge all required fees, fees under 37 CFR § 1.17 and all required extension of time fees, or credit any overpayment, to Jones Day U.S. Deposit Account No. 50-3013 (order no. 101962-999032).

Respectfully submitted,

Date: July 12, 2004



56,056

David C. Pauling (Reg. No.)
For: Nikolaos C. George (Reg. No. 39,201)
JONES DAY
222 East 41st Street
New York, NY 10017
(212) 326-3939